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Statin use and prostate inflammation in men with a negative prostate biopsy: results from the REDUCE trial

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Abstract

Statin use is associated with lower advanced prostate cancer risk. In addition to cholesterol-lowering, statins have systemic anti-inflammatory properties. However, their effect on histological prostate inflammation is not well understood, particularly among men at increased prostate cancer risk but with a negative prostate biopsy. We examined associations between serum lipid levels, statin use and histological prostate inflammation using data from 6,655 men with a negative baseline prostate biopsy in the REduction by DUtasteride of prostate Cancer Events (REDUCE) trial. Statin use and lipid levels [total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), triglycerides] were assessed at baseline. Inflammation was assessed by central review. Logistic regression was used to examine the effect of lipids and statin use on presence and extent of chronic and acute prostate inflammation [none, moderate ($<20\%$), severe ($\geq 20\%$ biopsy cores)]. Chronic and acute inflammation affected 77% and 15% of men, respectively. Men with high HDL (≥ 60 vs. <40 mg/dl) had reduced presence of acute inflammation (OR 0.79; 95%CI 0.63-0.99), and were less likely to have severe acute inflammation (OR 0.66; 95%CI 0.45-0.97), but there were no other associations between lipids and inflammation. Statin users had reduced presence of chronic inflammation (OR 0.81; 95%CI 0.69-0.95), and were less likely to have severe chronic (OR 0.80; 95%CI 0.68-0.95) and severe acute inflammation (OR 0.73; 95%CI 0.53-1.00), relative to non-users. Given the possible role for inflammation in prostate cancer, the inverse association between statins and prostate inflammation suggests a mechanism linking statins with lower advanced prostate cancer risk.

Introduction

An increasing amount of epidemiologic and laboratory data support a role for statins in chemoprevention. Some of the strongest evidence comes from prostate cancer, where statin use is associated with reduced risk of advanced disease and lower prostate cancer-specific mortality [1]. Statins effectively lower serum cholesterol levels by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme for cholesterol synthesis in the liver. High serum cholesterol drives tumor growth in mouse models of prostate cancer [2, 3], and results from epidemiologic studies show that high serum cholesterol is associated with increased risk of biochemical recurrence [4, 5] and elevated prostate cancer-specific mortality [6-8]. Together, these findings support a role for cholesterol, and for cholesterol-lowering interventions, in prostate cancer [9]. In addition to targeted cholesterol-lowering effects, statins may also have off-target effects on the prostate via non-cholesterol mediated mechanisms [1]. Results from clinical trials demonstrate that statins lower C-reactive protein (CRP) levels in the serum [10, 11] and reduce cytokine production by circulating lymphocytes [12] independent of their cholesterol-lowering effects, showing that statins lower systemic inflammation. Our group previously reported that statin users had less histological inflammation in their prostate tumors than non-users [13], suggesting that statins can also lower inflammation in the prostate tumor. However, no studies, to our knowledge, have examined the effect of statin use and serum lipid levels on prostate inflammation in men without prostate cancer.

Histological evaluation of negative prostate biopsies from prostate cancer screening and prevention trials has revealed prostate inflammation in approximately 60% - 80% of asymptomatic men undergoing biopsy due to elevated PSA levels [14-16]. However, the factors contributing to prostate inflammation are largely unknown. Our group previously reported that smokers had higher levels of prostate inflammation [17], showing that lifestyle factors may influence prostate biology. In the present analysis, we evaluated associations between serum lipid levels, statin use and prostate inflammation in negative baseline prostate biopsies of men participating in the REduction by DUtasteride of Prostate Cancer Events (REDUCE) trial

[18]. We hypothesized that high serum cholesterol would be associated with increased prostate inflammation, while statin use would be associated with reduced prostate inflammation.

Materials and Methods

Study population

The REduction by DUtasteride of prostate Cancer Events (REDUCE) is a four year, multicenter, double-blind and placebo-controlled study, the details of which have been described previously [18]. Only baseline data prior to randomization were used for the present analysis. Briefly, men were eligible for the study if they were between 50 and 75 years of age, and had a serum PSA level of 2.5-10 ng/ml (if 50-60 years of age) or 3-10 ng/ml (if 60-75 years of age). Eligibility criteria also required men to have a single, negative biopsy (6-12 cores) within 6 months before enrollment (independent of trial protocol). Baseline biopsies were centrally reviewed to confirm a negative prostate cancer diagnosis. Men were excluded if they had a history of prostate cancer, high-grade intraepithelial neoplasia, atypical small acinar proliferation, a prostate volume >80 ml, had undergone previous prostate surgery, or had an International Prostate Symptom Score ≥ 25 or ≥ 20 while receiving α -blockers for treatment of benign prostatic hyperplasia.

Exposure assessment

At baseline, a detailed medical history was obtained including smoking, medical comorbidities, medication use and alcohol use. Total serum cholesterol, LDL, HDL and triglyceride levels were measured by Quest Diagnostic (Van Nuys, California, USA) at baseline before randomization. The vast majority of lipid values were obtained from serum drawn in the fasting state (99.8%). Recommended cut points for normal, borderline and abnormal serum levels (all in mg/dl) of total cholesterol (<200, 200-239, ≥ 240), low density lipoprotein (LDL; <130, 130-159, ≥ 160), high density lipoprotein (HDL; ≥ 60 , 40-59, <40) and triglycerides (<150, 150-199, ≥ 200) were implemented according to National Cholesterol

Education Program (NCEP)-Adult Treatment Panel (ATP) III guidelines [19]. Subjects reported all medications they were currently using at baseline, including lipid-lowering medications (statins, fibrates and ezetimibe). The majority of men reporting lipid-lowering medication use were statin users (n=1,229; 91%). Among statin users, the majority of men reported lipophilic statin use (simvastatin, lovastatin, fluvastatin, or atorvastatin; n=1,066; 87%). As such, we had insufficient numbers to conduct analysis stratified by statin type (i.e. lipophilic vs. hydrophilic) or by type of lipid-lowering medication (i.e. statin vs. non-statin). Data for dose and duration of statin use were unavailable. Therefore, we treated statin use versus statin non-use at baseline as our exposure variable, regardless of non-statin lipid-lowering medication use.

Outcome assessment

The presence and extent of histologic prostatic inflammation was assessed by central review of baseline negative biopsies. Chronic inflammation consisted mainly of lymphocytes and variable number of plasma cells and macrophages. Acute inflammation consisted of neutrophils. We calculated the extent of chronic inflammation and acute inflammation by dividing the number of biopsy cores with chronic and acute inflammation, respectively, by the total number of biopsy cores. Percent chronic and acute inflammation were each subsequently categorized as none, moderate ($>0\%$ - $<20\%$ of biopsy cores), and severe ($\geq 20\%$ of biopsy cores). Cut points were selected to ensure sufficient numbers of participants in each category for analysis.

Statistical analysis

Of the 8,122 men included in the efficacy population, we excluded men with a baseline PSA <2.5 ng/ml or >10 ng/ml (n=112). We also excluded men with missing data for race (n=82), body mass index (BMI; n=127), smoking status (n=3), and serum lipid levels (n=1,143), resulting in n=6,655 men included in the present analysis. As shown in Supplementary Table 1, men excluded due to missing lipid levels were less likely to be white, less likely to be North American, and less likely to use statins and non-steroidal anti-

inflammatory drugs (NSAIDs). However, age, BMI or diabetes status did not differ between groups, nor did alcohol use or smoking status. Men with and without lipid data had similar prevalence of chronic prostate inflammation, but men with missing lipid data were more likely to have acute prostate inflammation.

Differences in baseline characteristics according to the presence of chronic and acute prostate inflammation and according to statin use were examined using Student's t tests and χ^2 tests for continuous and categorical variables, respectively, and Kruskal-Wallis tests for continuous variables not normally distributed.

Logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for associations between serum lipid levels (borderline or abnormal levels vs. normal levels), statin use (vs. non-use) and the presence and extent of chronic and acute prostate inflammation. All models were adjusted for age at baseline (continuous), race (white, non-white), geographic region (North America, Europe, other), BMI (continuous, log-transformed), smoking status (never, former, current), and NSAID use. Models examining associations between serum lipids and prostate inflammation produced similar findings whether or not we further adjusted for statin use, and thus, we chose to present findings adjusted for statin use. We also explored further adjusting models examining associations between statin use and prostate inflammation for serum lipid levels but this did not alter our findings and therefore these findings are not presented. In sensitivity analyses, we excluded men using any lipid-lowering medications (statins, fibrates, ezetimibe) from our analyses of associations between serum lipid levels and prostate inflammation. Finally, we explored excluding men using non-statin lipid-lowering medications (n=180) from our analysis of associations between statin use and inflammation but this produced similar findings and so these results are not presented.

Statistical analysis was performed using Stata, version 13.0 (Stata Corp., College Station, TX, USA).

Results

Demographic characteristics of men with and without histologic prostate inflammation

Chronic and acute prostate inflammation was detected in negative baseline prostate biopsies from 5,151 (77%) and 1,005 (15%) men enrolled in the REDUCE trial, respectively. Men with chronic prostate inflammation were older at the time of enrollment, less likely to be white, less likely to be European and less likely to report heavy alcohol use relative to those without chronic prostate inflammation (Table 1). Men with acute prostate inflammation were younger at the time of enrollment, less likely to be European and more likely to be current smokers than those without acute prostate inflammation. However, there were no differences in race or alcohol intake by acute inflammation status. Median BMI did not differ by either chronic or acute prostate inflammation status, and the prevalence of diabetes and NSAID use was similar in men with and without chronic and acute prostate inflammation (Table 1).

Demographic characteristics of men according to statin use

Of a total of 6,655 participants in this analysis, 1,217 (18%) were statin users (Table 2). Relative to non-users, statin users were older at time of enrollment, more likely to be white, and more likely to be North American. Statin users also had higher BMI, and a higher prevalence of diabetes than non-users. Finally, statin users were more likely to also use NSAIDs, but less likely to be current smokers than non-users. The prevalence of alcohol use did not differ significantly by statin use (Table 2).

Associations between serum lipid levels and prostate inflammation

Serum lipid levels were not associated with either the presence or extent of chronic prostate inflammation (Table 3). Neither were serum levels of total cholesterol, LDL or triglycerides associated with the presence or extent of acute inflammation (Table 4). However, relative to men with low HDL levels (<40 ng/ml), those with high HDL (≥ 60 ng/ml) were less likely to have acute prostate inflammation (OR_{any vs. none} 0.79; 95% CI 0.63-0.99), although the trend across HDL categories did not reach statistical significance (p-trend=0.071). Men with high HDL were also less likely to have severe acute

inflammation, defined as the presence of acute inflammation in $\geq 20\%$ of biopsy cores ($OR_{\text{severe vs. none}} 0.66$; 95% CI 0.45-0.97; Table 4). Restricting our analyses to men who were not using any lipid-lowering medications produced similar findings (Supplementary Tables 2 and 3).

Associations between statin use and prostate inflammation

Relative to non-users, statin users were less likely to have chronic prostate inflammation ($OR_{\text{any vs. none}} 0.81$; 95% CI 0.69-0.95), and the magnitude of this association was similar regardless of the extent of chronic inflammation ($OR_{\text{moderate vs. none}} 0.82$; 95% CI 0.68-0.99 and $OR_{\text{severe vs. none}} 0.80$; 95% CI 0.68-0.95; Table 5). Although statin use was not associated with the presence of acute inflammation ($OR_{\text{any vs. none}} 0.97$; 95% CI 0.81-1.17), statin users were less likely to have severe acute inflammation than non-users ($OR_{\text{severe vs. none}} 0.73$; 95% CI 0.53-1.00; $p=0.052$), although this association was borderline significant.

Discussion

The prevalence of statin use has increased rapidly over the past few decades and these medications are currently used by almost 30% of US adults [20]. In addition to their targeted cholesterol-lowering properties, statins reduce systemic inflammation [10] and have also been associated with reduced inflammatory infiltrate in prostate tumors [13]. However, direct effects of statins on histological inflammation in the benign prostate have not been described. Using data from 6,655 men with a negative baseline prostate biopsy participating in the REDUCE trial, we report that statin use was associated with reduced presence and extent of chronic prostate inflammation and reduced extent of acute prostate inflammation.

A state of chronic inflammation has been suggested to play a role in the development of many different cancer types, including prostate [21, 22]. However, the clinical significance of histological prostate inflammation remains controversial. Findings from the Prostate Cancer Prevention Trial (PCPT) showed that histological inflammation in benign prostate tissue was positively associated with concomitant co-

existence of high grade prostate cancer [16], with similar results seen in another small US biopsy study [23]. In contrast, data from REDUCE showed that the presence of histological inflammation in benign prostate tissue was inversely associated with prostate cancer risk upon subsequent biopsy [14]. An inverse association between benign prostate inflammation and prostate cancer risk has also been reported by a number of other epidemiologic studies [15, 24-26]. With the exception of PCPT where histological inflammation was assessed in PSA-independent prostate biopsies, all other studies evaluated the presence of histological inflammation in PSA-driven prostate biopsies. Among men with an elevated PSA but a negative biopsy, the elevated PSA may be due either to prostate inflammation or to undetected prostate cancer. Thus, men with an elevated PSA that is caused by inflammation may be at lower risk for prostate cancer detection upon re-biopsy, compared to their counterparts with an elevated PSA caused by occult prostate cancer. Since benign prostate tissue is difficult to obtain in the absence of a PSA-driven biopsy, the true direction of this association will be difficult to resolve. Given the null association between statin use and risk of either total or high grade prostate cancer in REDUCE [27], the clinical implications of our observed inverse association between statin use and histological prostate inflammation cannot be determined by the present study, and require further investigation.

Inflammation of benign prostate tissue is common, affecting 60-80% of men, but few lifestyle factors influencing prostate inflammation have been identified. Using REDUCE data, we previously reported a higher prevalence of histological prostate inflammation in current versus former or never smokers [17], and a case-control study nested in the placebo arm of the PCPT reported that serum fatty acid levels were linked with prostate inflammation [28], showing that diet and lifestyle factors can impact prostate inflammation. Statins reduce PSA levels [29, 30], and use of these medications has been inversely associated with benign prostatic enlargement and lower urinary tract symptoms [31, 32], suggesting that statins also directly influence prostate biology. Inflammation has been suggested as one potential mechanism contributing to these effects [33-35]. Indeed, results from clinical trials have shown that statins have systemic anti-inflammatory properties over and above their cholesterol-lowering function

[10, 11], and studies have also shown tissue-specific anti-inflammatory effects of statins, in adipose tissue [36] and in the vascular wall [37]. However, this study is the first, to our knowledge, to show that statins may have anti-inflammatory effects in benign prostate tissue. With the exception of an inverse association between high HDL and acute prostate inflammation, serum lipid levels were not associated with histological prostate inflammation, suggesting that cholesterol-independent effects of statins may underlie the association with prostate inflammation.

Our findings should be considered in the context of the strengths and weaknesses of this study. First, although on-study biopsies in REDUCE occurred independent of PSA levels or PSA changes, the baseline biopsies, which were analyzed in this study, were largely carried out due to elevated PSA levels. As such, these results cannot be used to infer the relationship between statin use and histologic prostate inflammation in men without a PSA-driven biopsy. In addition, eligibility criteria for REDUCE ensured that all men had baseline PSA levels between 2.5 and 10 ng/ml. Thus, these data cannot be used to infer the association between statin use and inflammation in men with normal PSA values. In addition, men with high-grade intraepithelial neoplasia, atypical small acinar proliferation, or those with a prostate volume >80 mL or those who had undergone previous prostate surgery or those who had an International Prostate Symptom Score ≥ 25 or ≥ 20 while receiving α -blockers were excluded. Although these exclusions increase the homogeneity of the sample, they may limit the generalizability of our results. Finally, we lacked data for dose and duration of statin use, precluding dose-response analyses. Study strengths include the large, multinational population in REDUCE. Moreover, histological inflammation was centrally reviewed by a single pathologist using prostate biopsies confirmed to be negative for prostate cancer, whereas prior studies evaluated inflammation in benign regions of the prostate adjacent to prostate cancer [16, 24]. This enables us to identify risk factors for histological prostate inflammation while ruling out inflammation as a response to the tumor.

To conclude, epidemiologic and laboratory data strongly support an inverse association between statin use and risk of advanced prostate cancer, and improving our understanding of the mechanisms contributing to

this inverse association will inform advanced prostate cancer prevention efforts [1]. Using baseline data from the REDUCE trial, we report that statin use was associated with reduced presence and extent of histological prostate inflammation among men with a negative prostate biopsy. The interpretation of these findings with respect to prostate cancer risk is somewhat challenging given the inverse association between histological inflammation and prostate cancer risk in REDUCE that may be attributable, at least in part, to selection bias induced by PSA-driven baseline biopsies [14]. The only study, to our knowledge, that avoided this potential source of bias by obtaining PSA-independent biopsies reported a positive association between histological prostate inflammation and prostate cancer risk [16]. In the context of that study, in addition to a body of work linking inflammation with increased prostate cancer risk [38], our findings suggest that reduction of prostate inflammation could contribute to the inverse association between statin use and risk of advanced prostate cancer.

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Table 1: Demographic characteristics of REDUCE participants according to the presence of chronic and acute prostate inflammation at baseline

	Chronic prostatic inflammation			Acute prostatic inflammation		
	Absent N=1,504 (23%)	Present N=5,151 (77%)	p value	Absent N=5,650 (85%)	Present N=1,005 (15%)	p value
Age, mean (SD)	62.2 (6.1)	62.8 (6.0)	0.0006	62.8 (6.0)	62.1 (6.1)	0.0002
Race, n (%)						
White	1,400 (93)	4,698 (91)	0.021	5,177 (92)	921 (92)	0.989
Non-white	104 (7)	453 (9)		473 (8)	84 (8)	
Region, n (%)						
N. America	336 (22)	1,562 (30)	<0.0001	1,496 (26)	402 (40)	<0.0001
Europe	990 (66)	2,947 (57)		3,405 (60)	532 (53)	
Other	178 (12)	642 (12)		749 (13)	71 (7)	
BMI (kg/m²), median (IQR)	26.8 (24.8-29.0)	26.9 (24.9-29.4)	0.277	26.9 (24.9-29.4)	26.9 (24.8-29.3)	0.766
Diabetes, n (%)						
No	1,369 (91)	4,726 (92)	0.373	5,174 (92)	921 (92)	0.944
Yes	135 (9)	425 (8)		476 (8)	84 (8)	
Statin use, n (%)						
No	1,212 (81)	4,226 (82)	0.198	4,632 (82)	806 (80)	0.178
Yes	292 (19)	925 (18)		1,018 (18)	199 (20)	
NSAID use, n (%)						
No	1,075 (71)	3,629 (70)	0.443	4,011 (71)	693 (69)	0.191
Yes	429 (29)	1,522 (30)		1,639 (29)	312 (31)	
Alcohol use, n (%)						
None	360 (24)	1,372 (27)	0.040	1,472 (26)	260 (26)	0.693
Moderate	720 (48)	2,463 (48)		2,692 (48)	491 (49)	
Heavy	417 (28)	1,292 (25)		1,461 (26)	248 (25)	
Smoking status, n (%)						
Never	698 (46)	2,321 (45)	0.124	2,580 (46)	439 (44)	0.001
Former	604 (40)	2,028 (39)		2,257 (40)	375 (37)	
Current	202 (13)	802 (16)		813 (14)	191 (19)	

*data for alcohol use was missing for n=31 participants

Table 2: Demographic characteristics of REDUCE participants according to statin use

	Statin use		<i>p value</i>
	No N=5,438 (82%)	Yes N=1,217 (18%)	
Age, mean (SD)	62.6 (6.0)	63.1 (6.1)	0.005
Race, n (%)			
White	4,964 (91)	1,134 (93)	0.031
Non-white	474 (9)	83 (7)	
Region, n (%)			
N. America	1,274 (23)	624 (51)	<0.0001
Europe	3,398 (62)	539 (44)	
Other	766 (14)	54 (4)	
BMI (kg/m²), median (IQR)	26.8 (24.7-29.1)	27.4 (25.4-30.1)	0.0001
Diabetes, n (%)			
No	5,063 (93)	1,032 (85)	<0.0001
Yes	375 (7)	185 (15)	
NSAID use, n (%)			
No	4,207 (77)	497 (41)	<0.0001
Yes	1,231 (23)	720 (59)	
Alcohol use, n (%)			
None	1,383 (26)	349 (29)	0.054
Moderate	2,630 (49)	553 (46)	
Heavy	1,400 (26)	309 (26)	
Smoking status, n (%)			
Never	2,546 (47)	473 (39)	<0.0001
Former	2,052 (38)	580 (48)	
Current	840 (15)	164 (13)	

*data for alcohol use was missing for n=31 participants

Table 3: Odds ratios for associations between serum lipid levels and the presence and extent of baseline chronic prostate inflammation in REDUCE

	Presence of chronic inflammation			Extent of chronic inflammation				
	None n	Any n	OR (95% CI)	None n	Moderate; < 20% of cores n	OR (95% CI)	Severe; ≥ 20% of cores n	OR (95% CI)
Total cholesterol								
<200 mg/dl	264	998	1	264	379	1	605	1
200-239 mg/dl	908	3,055	0.94 (0.80-1.09)	908	1,153	0.92 (0.77-1.10)	1,866	0.95 (0.80-1.12)
≥240 mg/dl	332	1,098	0.92 (0.76-1.11)	332	406	0.89 (0.71-1.10)	681	0.95 (0.77-1.16)
<i>p-trend</i>			0.657			0.501		0.854
LDL								
<130 mg/dl	733	2,591	1	733	969	1	1,583	1
130-159 mg/dl	424	1,496	1.03 (0.90-1.19)	424	568	1.04 (0.88-1.23)	917	1.05 (0.90-1.22)
≥160 mg/dl	347	1,064	0.94 (0.80-1.10)	347	401	0.93 (0.78-1.12)	652	0.95 (0.80-1.12)
<i>p-trend</i>			0.285			0.313		0.374
HDL								
<40 mg/dl	271	1,053	1	271	404	1	636	1
40-59 mg/dl	943	3,139	0.89 (0.77-1.04)	943	1,179	0.87 (0.73-1.04)	1,921	0.90 (0.77-1.07)
≥60 mg/dl	290	959	0.91 (0.75-1.11)	290	355	0.88 (0.70-1.11)	595	0.94 (0.76-1.15)
<i>p-trend</i>			0.993			0.857		0.848
Triglyceride								
<150 mg/dl	953	3,326	1	953	1,253	1	2,038	1
150-199 mg/dl	279	956	1.00 (0.86-1.17)	279	363	1.00 (0.84-1.20)	575	0.99 (0.84-1.17)
≥200 mg/dl	272	869	0.93 (0.79-1.09)	272	322	0.90 (0.75-1.09)	539	0.94 (0.80-1.12)
<i>p-trend</i>			0.329			0.276		0.508

ORs were adjusted for age at baseline (continuous), race (white, non-white), geographic region (North America, Europe, other), BMI (continuous, log-transformed), smoking status (never, former, current), statin use (no, yes), and NSAID use (no, yes)

Table 4: Odds ratios for associations between serum lipid levels and presence and extent of baseline acute prostate inflammation in REDUCE

	Presence of acute inflammation			Extent of acute inflammation				
	None n	Any n	OR (95% CI)	None n	Moderate; < 20% of cores n	OR (95% CI)	Severe; ≥ 20% of cores n	OR (95% CI)
Total cholesterol								
<200 mg/dl	1,067	195	1	1,067	125	1	67	1
200-239 mg/dl	3,364	599	1.06 (0.89-1.27)	3,364	398	1.08 (0.87-1.34)	195	1.04 (0.78-1.39)
≥240 mg/dl	1,219	211	1.09 (0.87-1.35)	1,219	150	1.18 (0.91-1.52)	61	0.96 (0.67-1.39)
<i>p-trend</i>			0.669			0.313		0.655
LDL								
<130 mg/dl	2,802	522	1	2,802	352	1	165	1
130-159 mg/dl	1,645	275	0.97 (0.82-1.15)	1,645	181	0.95 (0.78-1.16)	91	1.00 (0.76-1.32)
≥160 mg/dl	1,203	208	1.04 (0.86-1.25)	1,203	140	1.04 (0.83-1.29)	67	1.07 (0.78-1.46)
<i>p-trend</i>			0.556			0.584		0.670
HDL								
<40 mg/dl	1,105	219	1	1,105	139	1	79	1
40-59 mg/dl	3,460	622	0.92 (0.78-1.09)	3,460	419	0.97 (0.79-1.19)	196	0.81 (0.62-1.07)
≥60 mg/dl	1,085	164	0.79 (0.63-0.99)	1,085	115	0.86 (0.66-1.13)	48	0.66 (0.45-0.97)
<i>p-trend</i>			0.071			0.248		0.120
Triglyceride								
<150 mg/dl	3,639	640	1	3,639	418	1	215	1
150-199 mg/dl	1,054	181	1.00 (0.84-1.20)	1,054	126	1.08 (0.87-1.34)	54	0.87 (0.64-1.19)
≥200 mg/dl	957	184	1.11 (0.92-1.33)	957	129	1.20 (0.97-1.49)	54	0.95 (0.69-1.30)
<i>p-trend</i>			0.268			0.118		0.884

ORs were adjusted for age at baseline (continuous), race (white, non-white), geographic region (North America, Europe, other), BMI (continuous, log-transformed), smoking status (never, former, current), statin use (no, yes), and NSAID use (no, yes)

Table 5: Odds ratios for associations between statin use and presence and extent of baseline prostate inflammation in REDUCE

	Presence of chronic inflammation			Extent of chronic inflammation				
	None n	Any n	OR (95% CI)	None n	Moderate; < 20% of cores n	OR (95% CI)	Severe; ≥ 20% of cores n	OR (95% CI)
Statin use								
No	1,212	4,226	1	1,212	1,592	1	2,582	1
Yes	292	925	0.81 (0.69-0.95)	292	346	0.82 (0.68-0.99)	570	0.80 (0.68-0.95)
	Presence of acute inflammation			Extent of acute inflammation				
	None n	Any n	OR (95% CI)	None n	Moderate; < 20% of cores n	OR (95% CI)	Severe; ≥ 20% of cores n	OR (95% CI)
Statin use								
No	4,632	806	1	4,632	530	1	269	1
Yes	1,018	199	0.97 (0.81-1.17)	1,018	143	1.11 (0.90-1.38)	54	0.73 (0.53-1.00)

ORs were adjusted for age at baseline (continuous), race (white, non-white), geographic region (North America, Europe, other), BMI (continuous, log-transformed), smoking status (never, former, current), NSAID use (yes, no)